Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Progressive Brain Atrophy in Alternating Hemiplegia of Childhood

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Abstract: **Background:** Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder that includes involuntary movements, paroxysmal symptoms, and various severities of nonparoxysmal symptoms.

Objective: To investigate the occurrence of structural brain abnormalities in patients with AHC during clinical courses.

Methods: Conventional brain magnetic resonance imaging findings and clinical courses were retrospectively investigated in 14 patients with AHC confirmed by *ATP1A3* mutations.

Results: Progressive frontal dominant cerebral, diffuse cerebellar cortical, and severe hippocampal atrophy were observed in seven patients with irreversible severe motor and intellectual deterioration. All of these seven patients exhibited status epilepticus and required transient respiratory care. Isolated diffuse cerebellar cortical atrophy was observed in two adult patients with mild motor regression. Five patients without apparent deterioration displayed almost normal brain findings.

Conclusions: The areas of atrophy were consistent with the areas of increased expression of the Na^+/K^+-ATPase α3 subunit encoded by *ATP1A3*. Some of paroxysmal and nonparoxysmal neurological symptoms are considered as related to the areas of brain atrophy.

Introduction

Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental disorder, characterized by involuntary movements (dystonia, choreoathetosis), paroxysmal symptoms (recurrent flaccid or dystonic hemiplegic episodes, abnormal ocular movements, seizures), and various severities of nonparoxysmal symptoms (mental retardation, hypotonia, ataxia).[1–3] AHC is caused by heterozygous Na^+/K^+-ATPase α3 subunit gene (*ATP1A3*) mutations.[4–6] The *ATP1A3* mutation was originally found in rapid-onset dystonia-parkinsonism (RDP). AHC and RDP are thought to be part of a spectrum of *ATP1A3*-related disorders.[7] More recently, a few new phenotypes[8–10] have been reported.

Even in AHC, disease severity is variable with some patients exhibiting severe motor and intellectual deterioration. Brain magnetic resonance imaging (MRI) usually shows no specific abnormal findings in patients with AHC, at least early in the course of the disease.[2,3,11] Therefore, it has been postulated that conventional brain MRI is not useful for diagnosing AHC. Consequently, there is little knowledge regarding the structural changes in the brain during the clinical course of this disease. Some studies reported nonspecific cerebral atrophy, generalized cortical atrophy, mesial temporal sclerosis, or cerebellar atrophy in a few cases.[2,12,13] However, the relationship between the clinical course and changes in brain MRI findings has not yet been established in patients with AHC. The precise cause of these clinical variabilities in AHC is not yet known except for partial correlations between the genotype and phenotype as reported by several groups.[14–17]

We found progressive localized brain atrophy in some patients, particularly where severe deterioration was evident.[18,19] We investigated Japanese patients with AHC to assess if they had structural brain abnormalities and to determine the critical

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Keywords: MRI, cerebellar atrophy, hippocampal sclerosis, cerebral atrophy, ATP1A3.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 30 June 2016; revised 8 September 2016; accepted 14 September 2016.
Published online 05 January 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12451

doi:10.1002/mdc3.12451

brain structural differences between a group with irreversible severe deterioration and one without severe deterioration.

Methods

All participants in this study were diagnosed by the use of previously described clinical criteria[1,2] and by genetic confirmation. As previously described, genetic analysis confirmed the presence of *ATP1A3* mutations in participants.[14] Brain MRI/computed tomography (CT) findings and information on the clinical course of disease were retrospectively analyzed. We compared the neuroradiological findings, clinical courses of disease, and *ATP1A3* genotypes among these patients.

The ethical committee of the National Center of Neurology and Psychiatry approved this study. Written informed consent was obtained from the patients' parents.

Results

Twelve patients from the previous study[14] participated in this study, and two newly diagnosed patients were included. *ATP1A3* mutations and clinical findings of each case are shown in Table 1.

Seven of 14 patients, aged 14–35 years, had irreversible severe motor and intellectual deterioration (Cases 1–7: c.2443G>A, p.Glu815Lys, n = 6 and c.2263G>A, p.Gly755Ser, n = 1). Among the remaining seven patients (Cases 101–107: p.Glu815Lys, n = 2; c.2401G>A, p.Asp801Asn, n = 2; c.2263G>T, p.Gly755Cys, n = 1; c.2423C>T, p.Pro808Leu, n = 1; and c.2767G>A, p.Asp923Asn, n = 1), aged 6–46 years, two showed mild motor regression (Cases 101 and 102) and there was no apparent long-term motor or intellectual deterioration in the other five.

All seven patients with irreversible severe deterioration displayed abnormal brain MRI findings including frontal dominant cerebral, severe hippocampal, and diffuse cerebellar cortical atrophy (Fig. 1). However, MRI or CT scan at the first examination during early childhood showed normal brain morphology in all of these patients. Therefore, all of these patients demonstrated progressive brain atrophy. All patients with severe deterioration had experienced status epilepticus and required transient respiratory care before the latest MRI study. Three patients continue to require the use of a respirator (Table 1).

In the remaining seven patients, four patients aged 7–21 years, with no apparent motor or intellectual deterioration, displayed no abnormal brain MRI findings. Two adult patients (Cases 101 and 102), aged 30 and 46 years, respectively, with mild motor regression, showed diffuse cerebellar cortical atrophy (Fig. 2). In a patient with the p.Asp801Asn mutation (Case 104), a right hippocampal swelling was identified just after status epilepticus was confirmed at 8 years.[12] The patient demonstrated transient regression and recovered within 2 months. He suffered from temporal lobe epilepsy, and mild right hippocampal sclerosis was detected at 16 years. Two patients experienced status epilepticus and the frequencies of it were lower than those in patients with brain atrophy.

Discussion

Patients with AHC can deteriorate either abruptly or gradually at the motor and intellectual function level.[12,14,20] Before this study, we postulated that there might be nonspecific brain atrophy even in patients with AHC who are exhibiting severe deterioration.[2,11,12,14,18] After assessing the conventional brain MRI findings and genotypes of our patients, we have shown for the first time that similar abnormal findings exist in patients with severe deterioration. Progressive brain atrophy and cerebellar atrophy/ataxia have been reported in a spectrum of *ATP1A3*-related disorders other than AHC.[8–10]

Seven patients, six of whom had the p.Glu815Lys mutation, with irreversible severe motor and intellectual deterioration, exhibited similar brain abnormalities. All of these seven patients experienced status epilepticus and required transient respiratory care. These included frontal dominant cerebral, bilateral severe hippocampal, and diffuse cerebellar cortical atrophy. Given that these findings were evident in all seven patients with severe deterioration, this triad of abnormal findings could be considered as characteristic abnormal cerebral findings in patients with AHC exhibiting severe deterioration.

These findings might be related to those observed in severe hypoxic events or status epilepticus. Typical brain findings in severe hypoxic events include diffuse cerebral cortical atrophy (laminar cortical necrosis), particularly in the watershed zone, and basal ganglia necrosis.[21] The hippocampus and cerebellar Purkinje cells are also vulnerable to hypoxia or status epilepticus.[22] Because there is a lack of necrosis in cortical laminae and basal ganglia, the atrophic areas in severe AHC in this MRI study are not typical findings compared to general hypoxic events.

Frontal cerebral, hippocampal, and cerebellar cortical atrophy could only be related to status epilepticus, because all patients with severe deterioration exhibited several episodes of status epilepticus. Frontal cerebral, hippocampal, and cerebellar cortical atrophy can be caused by status epilepticus.[22] We observed transient hippocampal swelling in one case.[12] Because status epilepticus is an energy-consumption event, it is possible that many neurons in the frontal cortex, hippocampus, and cerebellar cortex could be damaged.

In addition, we observed cerebellar cortical atrophy in two adult patients with mild motor deterioration and without status epilepticus. Cerebellar cortical atrophy was demonstrated in the natural course of AHC. Therefore, we postulate that there is an additional reason for these similar atrophies occurring in some patients with AHC. The expression of the Na^+/K^+-ATPase $\alpha 3$ subunit has been known to occur only in neurons, especially of the neocortical pyramidal, hippocampal pyramidal, cerebellar Purkinje cells, and basal ganglia according to studies in rodents.[23–27] The progressive atrophic areas of the brain found in our study might be related to the amount of the expression of the Na^+/K^+-ATPase $\alpha 3$ subunit in neurons. Consequently, we are relatively sure that these critical atrophic findings are related to the cause of irreversible deterioration.

doi:10.1002/mdc3.12451

TABLE 1 Mutation Type and Clinical Findings for Each Case

Case No.	No. in Ref. 14	*ATP1A3* Mutation	Sex	Age (yr)	Seizures	Status Epilepticus (Onset)	Flunarizine Medication (Administration Period)	Motor and Intellectual Deterioration (Period)	Motor Level	Cognitive Level	Involuntary Movement	Respiratory Care	Age at MRI (yr)	MRI (CT) Findings
1	G-1-01	p.E815K	F	35	(+)	(+) (~5 yr)	D (2–4 yr)	(+) (6 yr)	Stand	Words	A, Dys	R, T	5 (CT)	N
									Bed	Profound			30	F, C, H
2	New	p.E815K	F	29	(+)	(+) (~10 yr)	D (2–10 yr)	(+) (20 yr)	Bed	Profound	A, Dys		20 (CT)	F, C, H
3	G-1-02	p.E815K	M	18	(+)	(+) (~6 yr)	D (3–5 yr)	(+) (6 yr)	Sit	Sentence	A, Dys		3	N
									Bed	Words			16	F, C, H
4	G-1-04	p.E815K	M	16	(+)	(+) (~6 yr)	D (3–6 yr)	(+) (7 yr)	Stand	Words	A, Dys	R, T	2	N,
									Bed	Words			16	F, C, H
5	G-1-05	p.E815K	M	16	(+)	(+) (~3 yr)	D (1–3 yr)	(+) (4 yr)	Stand	Words	A, Dys		2	N
									Bed	Profound			15	F, C, H
6	G-3-07	p.G755S	M	15	(+)	(+) (~10 yr)	D (1–5 yr)	(+) (12 yr)	Stand	Words	A, Dys	R, T	3	N
									Bed	Profound			13	F, C, H
7	G-1-06	p.E815K	M	14	(+)	(+) (~2 yr)	(N–)	(+) (3 yr)	Sit	Words	A, Dys		1	F, C, H
									Bed	Profound			12	
101	G-2-01	p.D801N	F	46	(–)	(–)	D (15–16 yr)	(+) (30 yr)	Walk	Sentence	A, Dys		30	C, mild
								Mild regression	Stand	Sentence			46	C
102	New	p.P808L	F	30	(+)	(–)	D (1–5 yr)	(+) (25 yr)	Stand	Sentence	A, Dys		20	N
								Mild regression	Sit	Words			30	C
103	G-3-05	p.G755C	M	21	(+)	(+) (~10 yr)	(C+) 12 yr→	(–)	Walk	Sentence	A		18	N
104	G-2-07	p.D801N	M	16	(+)	(+) (~3 yr)	(C+) 3 yr→	(–)	Stand	Words	A, Dys		3	N
									Stand	Words			16	rt. H (sclerosis)
105	G-3-09	p.D923N	M	13	(–)	(–)	(C+) 7 yr→	(–)	Walk	Sentence	A, Dys		13	N
106	G-1-07	p.E815K	M	12	(+)	(–)	(C+) 2 yr→	(–)	Stand	Words	A		9	N
107	G-1-10	p.E815K	M	7	(+)	(–)	(C+) 4 yr→	(–)	Stand	Words	A		6	N

The group with deterioration, 1–7, and the group without deterioration, 101–107.
Flunarizine: D, discontinued; (N–), never used; (C+), continue to use.
Motor level: Bed, bedridden; Sit, sit without support; Stand, stand with support; Walk, walk unassisted.
Involuntary movement: A, ataxia; Dys, dystonia.
Respirator: R, respirator care; T, tracheotomy.
MRI findings: N, normal; F, frontal atrophy; C, cerebellar atrophy; H, hippocampal atrophy.

doi:10.1002/mdc3.12451

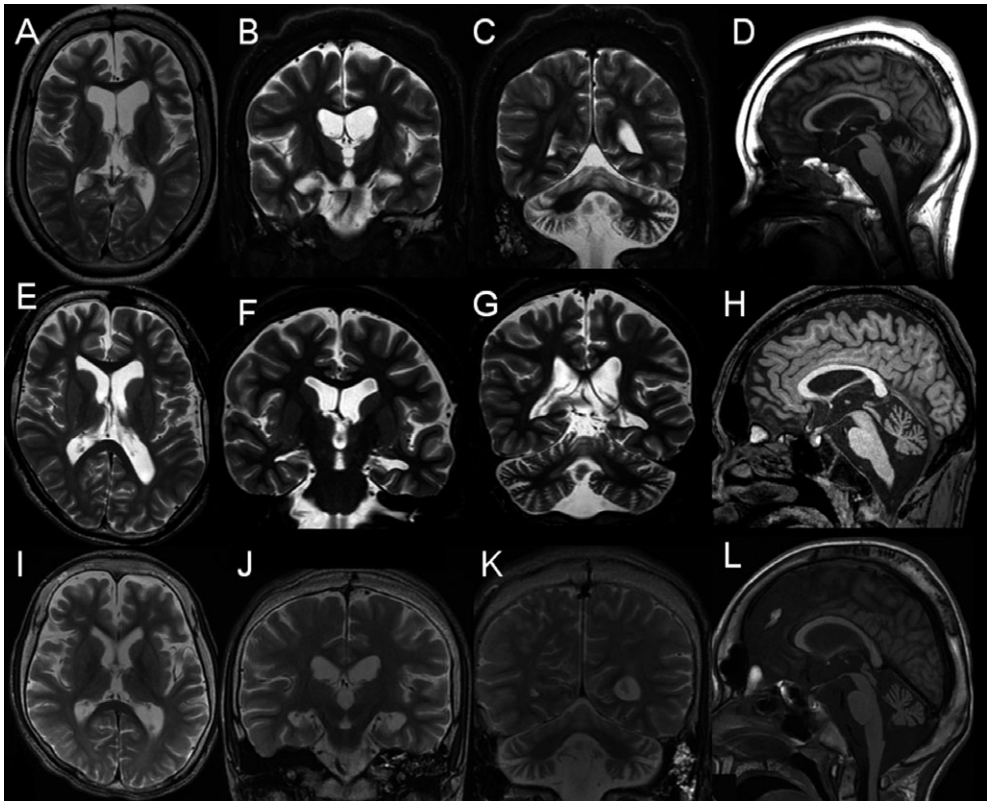

Figure 1 Brain MRI of Case 1 at 30 years (A, B, C, and D), Case 5 at 16 years (E, F, G, and H), and Case 6 at 12 years (I, J, K, and L). (T_2–weighted images: axial section, A, E, and I; coronal section, B, C, F, G, J, and K. T_1-weighted images: sagittal section, D, H, and L). Brain MRI shows cerebral atrophy, predominantly in the frontal lobes with enlargement of the lateral ventricles (A, E, and I), bilateral hippocampal atrophy with enlargement of the inferior horn of the lateral ventricles (B, F, and J), and diffuse cerebellar cortical atrophy (C, D, G, H, K, and L).

We speculate that neurons expressing the Na^+/K^+-ATPase α3 subunit are more susceptible to damage by energy-consuming events such as status epilepticus or fever because of impaired function of Na^+/K^+-ATPase. Therefore, these irreversible atrophic changes in the brain occurred in these areas in only some patients with AHC exhibiting severe irreversible deterioration. This was particularly true for those with the p.Glu815Lys mutation, which could be related to neuronal fragility. The precise reason why this mutation is related to the severe clinical phenotype has not yet been found.[14,28]

A postmortem neuropathological study in patients with AHC has not been reported. In the spectrum of abnormal conditions associated with *ATP1A3*, there has only been one report on patients with RDP with comorbid diseases (cerebrovascular and Alzheimer's disease).[29] This neuropathological study was the first one conducted on carriers of the *ATP1A3* mutation. Neuropathological findings of RDP may be similar to those of AHC because they could be allelic disorders.[1,7,30,31] Anatomical areas identified as potential targets of the p.Ile758Ser mutation were the globus pallidus, subthalamic nucleus, red nucleus, inferior olivary nucleus, cerebellar Purkinje and granule cell layers, and dentate nucleus. Involvement of subcortical white matter tracts was also evident. Their involvement may have caused an interruption of the cerebral and cerebellar connections, which are essential for maintenance of motor control. From our observations, cerebellar Purkinje and granule cell layers, pyramidal cells in the frontal cortex, and the hippocampus might be targets for several *ATP1A3* mutations in some patients with AHC. A special RDP patient who displayed cerebellar atrophy with *ATP1A3* and another gene mutation was recently reported.[32] When patients with *ATP1A3* mutations have cerebral or cerebellar atrophy, there could be any other gene mutations, some other epigenetic factors, or exogenous factors such as hypoxia.

Most patients with AHC show not only paroxysmal neurological symptoms but also nonparoxysmal neurological symptoms, which include hypotonia, intellectual disabilities, behavioral abnormalities, ataxia, involuntary movements, and other symptoms. These nonparoxysmal neurological symptoms could be caused by functional or organic neuronal abnormalities because of hyperexcitability or vulnerability of the neurons in the frontal cerebral cortex, hippocampus, and cerebellar cortex.[33] To prevent patients with AHC from not only hemiplegic

doi:10.1002/mdc3.12451

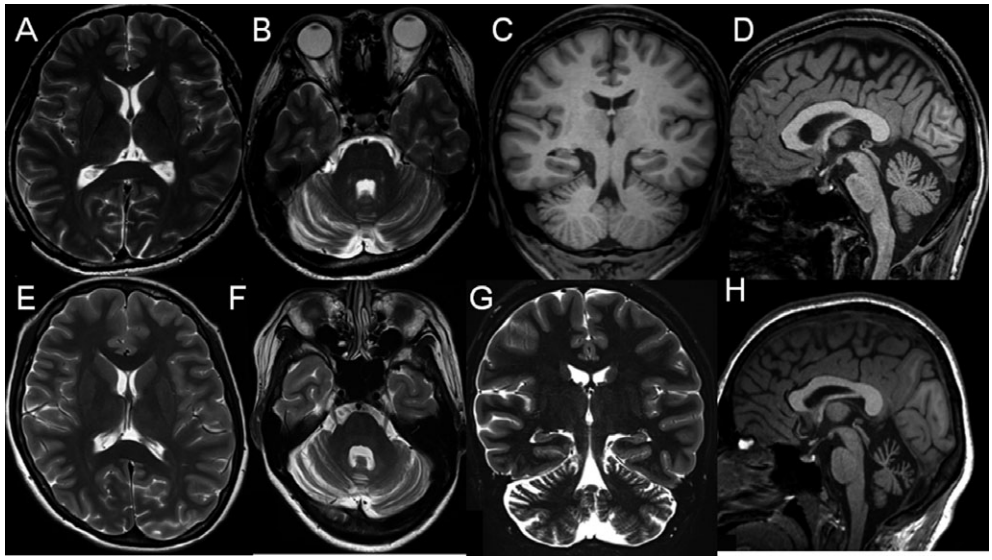

Figure 2 Brain MRI of Case 101 at 46 years (A, B, C, and D) and Case 102 at 30 years (E, F, G, and H). (T_2-weighted images: axial section, A, B, E, and F; coronal section, G. T_1-weighted images: coronal section, C; sagittal section, D and H). MRI displays cerebellar cortical atrophy but no cerebral atrophy in both cases.

attacks but also from severe deterioration, a new treatment method that could improve the function of the mutated Na^+/K^+-ATPase α3 subunit is necessary.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Performance of Literature Survey, D, Execution; (2) Statistical Analysis: A. Design, B. Obtaining of Clinical Data and Creation of Figures, C. Performance of Sanger Sequencing and Data Analyses for De Novo Single-Nucleotide Variants, D. Execution, E. Review and Critique; (3) Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

M.S.: 1A, 1C, 2A, 2B, 3A
A.I.: 1C, 2A, 2C, 3A
Y.S.: 1A, 1C, 2A, 2B, 3A
S.H.: 1C, 2A, 2C, 3A

Acknowledgments

We are grateful to the members of the Japanese AHC Family Association.

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This work was supported by the Intramural Research Grants (24-7 and 27-5) for Neurological and Psychiatric Disorders of NCNP (M.S., Y.S., and S.H.), Grant-in-Aid for Young Scientists (B) (23791201) (A.I.), Grants-in-Aid for Scientific Research (A) (24249060 and 151402548) (S.H.), Grants-in-Aid for Challenging Exploratory Research (25670481) (S.H.). This work was also supported by Bilateral Joint Research Projects (S.H.) from the Japan Society for the Promotion of Science (JSPS), Grants for Scientific Research on Innovative Areas (A.I and S.H.) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) (221S0002 and 25129708), the MEXT-supported Program for the Strategic Research Foundation at Private Universities 2013-2017 (S.H.), a grant for the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED) (15ek0109038a), a Grant-in-Aid for the Research on Measures for Intractable Diseases (H26-Nanji-Ippan-051 and 049) (S.H.) from the Ministry of Health, Labor and Welfare, the Joint Usage/Research Program of Medical Research Institute, Tokyo Medical and Dental University (S.H.), grants from the Mitsubishi Foundation (S.H.) and the Takeda Scientific Foundation (S.H.), the Kobayashi Magobei Foundation (A.I.), and the Kurozumi Medical Foundation (A.I.), and the Japan Epilepsy Research Foundation Grant (A.I.). The authors report no conflicts of interest.

Financial Disclosures for the previous 12 months: The authors report no sources of funding and no conflicts of interest.

doi:10.1002/mdc3.12451

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doi:10.1002/mdc3.12451